PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: George H. Yoo	Group Art Unit: 1633
Serial No.: 10/747,798	Examiner: Scott D. Priebe
Filed: December 29, 2003	Atty. Dkt. No.: INRP:104US
For: P53 TREATMENT OF PAPILLOMAVIRUS AND CARCINOGEN-TRANSFORMED CELLS IN HYPERPLASTIC LESIONS	

DECLARATION OF LOUIS ZUMSTEIN, PhD, UNDER 37 C.F.R. §1.132

I, Louis Zumstein, Ph.D., hereby declare as follows:

1. I have been employed by Introgen Therapeutics for over 10 years and my current position with this company is Associate Vice President of Research.

2. I have over 13 years of experience in the biotechnology field since 1993, including both research and preclinical drug development. Additionally my educational background includes a Ph.D. from Harvard University in biochemistry and molecular biology, and postdoctoral research at both Harvard University and Stanford University. A copy of my curriculum vita (or NIH biosketch) is attached as Appendix A.

3. I understand that the Examiner contends that a patent application (WO/99/66946) by El-Deiry indicates that p73 is a homolog of p53.

4. I have read the page 14, lines 5-10 of the instant specification which states:

> Throughout this application, the term "p53" is intended to refer to the exemplified p53 molecules as well as all p53 homologues from other species. "Wild-type" and "mutant" p53 refer, respectively, to

> a p53 gene expressing normal tumor suppressor activity and to a p53 gene lacking or having reduced suppressor activity and/or having transforming activity. Thus "mutant" p53 are not merely sequence variants but rather, are those variants showing altered functional profiles.

5. As a scientist in the biotechnology field, I feel that the aforementioned lines regarding p53 indicate that this passage is specific for human p53 and p53 in other species. I do not believe from reading this passage that "p53" as used in this passage would refer to proteins other than p53 that might share some functional characteristics with p53,.

6. Furthermore, as a scientist in the biotechnology field, it is my belief that p73 is not a homologue of p53. More specifically, while p73 and p53 do share some similar functions, and share some sequence similarities, there are important characteristics that distinguish the two proteins. For example, in contrast to p53 deficient mice, those mice lacking p73 show no increased susceptibility to spontaneous tumorigenesis. Additionally, p73 is not activated by DNA damage, unlike p53.

7. I hereby declare that all statements made by my own knowledge are true and all statements made on information and belief are believed to be true and further that statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment under § 100 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this application or any patent issued thereon.

_____17 February 2006_____ Date

_____ Louis Zumstein

BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Louis A. Zumstein	Associate Vice President, Research

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.*)

INSTITUTION AND LOCATION	DEGREE (*if applicable*)	YEAR(s)	FIELD OF STUDY
University of Miami, FL		1973-75	
Florida State Univ., Tallahassee, FL	BS	1975-1977	Biology
Harvard University, Cambridge, MA	Ph.D.	1978-1986	Biochemistry
Stanford University, Stanford, CA	Post-doc	1987-1991	Molecular Biology
Baylor College of Medicine	Post-Doc	1991-1993	Molecular Biology

Professional Experience:

2/2005 to present — Associate Vice President, Research, Introgen Therapeutics, Inc., Houston, TX 77030. Supervising pre-clinical development of three gene therapy products for oncology. Overall project leader for one gene therapy product for cancer, about to start clinical development.

4/1999 - 2/2005 — Director of Research, Introgen Therapeutics, Inc., Houston, TX 77030. Supervising pre-clinical development of three gene therapy products for oncology.

3/1997 - 4/1999 — Associate Director of Research, Introgen Therapeutics, Inc., Houston, TX 77054. Supervise group gathering pre-clinical data on two products. Project leader for Introgen's second product through IND submission.

3/1995 - 2/1997 — Research Program Manager, Vector Development, Introgen Therapeutics, Inc., Houston, TX 77054 Performed and supervised early production and process development work. Supervised clinical sample assay development, intimately involved in our Phase I HNSCC trial with RPR/INGN 201.

10/1993 - 2/1995 — Assistant Director of Research, Sennes Drug Innovations, Inc., Houston, TX 77054. Supervision of production group, and cell biology/assay development group.

Awards and Honors:

1977 — Phi Beta Kappa, Florida State University, Tallahassee, FL

1988 - 1991 — NSF Postdoctoral Research Fellowship in Plant Biology

Selected Publications:

Yoo GH, Piechocki MP, Oliver J, Lonardo F, Zumstein L, Lin HS, Kim H, Shibuya TY, Shehadeh N, Ensley JF. *Enhancement of Ad-p53 therapy with docetaxel in head and neck cancer.* Laryngoscope. 2004 Nov;114(11):1871-9.

Halloran CM, Ghaneh P, Shore S, Greenhalf W, Zumstein L, Wilson D, Neoptolemos JP, Costello E. *5-Fluorouracil or gemcitabine combined with adenoviral-mediated reintroduction of p16INK4A greatly enhanced cytotoxicity in Panc-1 pancreatic adenocarcinoma cells.* J Gene Med. 2004 May;6(5):514-25.

Saito Y, Gopalan B, Mhashilkar AM, Roth JA, Chada S, Zumstein L, Ramesh R. *Adenovirus-mediated PTEN treatment combined with caffeine produces a synergistic therapeutic effect in colorectal cancer cells.* Cancer Gene Ther. 2003 Nov;10(11):803-13.

Saito Y, Swanson X, Mhashilkar AM, Oida Y, Schrock R, Branch CD, Chada S, Zumstein L, Ramesh R. *Adenovirus-mediated transfer of the PTEN gene inhibits human colorectal cancer growth in vitro and in vivo.* Gene Ther. 2003 Nov;10(23):1961-9.

Stewart AL, Mhashilkar AM, Yang XH, Ekmekcioglu S, Saito Y, Sieger K, Schrock R, Onishi E, Swanson X, Mumm JB, Zumstein L, Watson GJ, Snary D, Roth JA, Grimm EA, Ramesh R, Chada S. *PI3 kinase blockade by Ad-PTEN inhibits invasion and induces apoptosis in RGP and metastatic melanoma cells.* Mol Med. 2002 Aug;8(8):451-61.

Saeki T, Mhashilkar A, Swanson X, Zou-Yang XH, Sieger K, Kawabe S, Branch CD, Zumstein L, Meyn RE, Roth JA, Chada S, Ramesh R. *Inhibition of human lung cancer growth following adenovirus-mediated mda-7 gene expression in vivo.* Oncogene. 2002 Jul 4;21(29):4558-66.

Mohiuddin I, Cao X, Ozvaran MK, Zumstein L, Chada S, Smythe WR. *Phosphatase and tensin analog gene overexpression engenders cellular death in human malignant mesothelioma cells via inhibition of AKT phosphorylation.* Ann Surg Oncol. 2002 Apr;9(3):310-6.

Ghaneh P, Greenhalf W, Humphreys M, Wilson D, Zumstein L, Lemoine NR, Neoptolemos JP. *Adenovirus-mediated transfer of p53 and p16(INK4a) results in pancreatic cancer regression in vitro and in vivo.* Gene Ther. 2001 Feb;8(3):199-208.

Kawabe S, Munshi A, Zumstein LA, Wilson DR, Roth JA, Meyn RE. *Adenovirus-mediated wild-type p53 gene expression radiosensitizes non-small cell lung cancer cells but not normal lung fibroblasts.* Int J Radiat Biol. 2001 Feb;77(2):185-94.

Jacobberger JW, Sramkoski RM, Zhang D, Zumstein LA, Doerksen LD, Merritt JA, Wright SA, Shults KE. *Bivariate analysis of the p53 pathway to evaluate Ad-p53 gene therapy efficacy.* Cytometry. 1999 Oct 15;38(5):201-13.

Zumstein LA, Lundblad V. *Telomeres: has cancer's Achilles' heel been exposed?* Nat Med. 1999 Oct;5(10):1129-30.

Clayman GL, el-Naggar AK, Lippman SM, Henderson YC, Frederick M, Merritt JA, Zumstein LA, Timmons TM, Liu TJ, Ginsberg L, Roth JA, Hong WK, Bruso P, Goepfert H. *Adenovirus-mediated p53 gene transfer in patients with advanced recurrent head and neck squamous cell carcinoma.* J Clin Oncol. 1998 Jun;16(6):2221-32.